

**In the Specification:**

Please amend the specification as shown:

Please delete the paragraph on page 6, lines 4-6 and replace it with the following paragraph:

In a further preferred embodiment of the present invention, the peptide is selected from the group consisting of cFLSYK(SEQ ID NO: 5), cFLSYR (SEQ ID NO: 6) and c (2NapA) LS (2NapA) R.

Please delete the paragraph on page 6, lines 8-10 and replace it with the following paragraph:

When used herein the term "cFLSYK" (SEQ ID NO: 5) means "cyclic FLSYK"(SEQ ID NO: 5), "cFLSYR" (SEQ ID NO: 6) means "cyclic FLSYR" (SEQ ID NO: 6) and "c(2NapA)LS(2NapA)R" means "cyclic (2Nap)LS (2Nap)R". The term "2NapA" is an abbreviation for 2-naphthylalanine.

Please delete the paragraph on page 8, line 18 to page 9, line 4 and replace it with the following paragraph:

Figure 2. Effect of exogenous addition of sPLA<sub>2</sub>-IIA on prostate cell growth. LNCaP cells were grown in RPMI with 5% FCS and treated for 72 hours in media containing (A) increasing concentrations of sPLA<sub>2</sub>-IIA alone (closed bars) or increasing concentrations of the activity-dead sPLA<sub>2</sub>-IIA mutant H<sub>48</sub>Q. (B) a fixed concentration of sPLA<sub>2</sub>-IIA and increasing concentrations of the sPLA<sub>2</sub>-IIA inhibitor cFLSYR (SEQ ID NO: 6). Cell number relative to untreated control cells was determined by the MTS assay as described in Materials and Methods. Data are Mean ± SD of quadruplicate determinations normalised to 100% for untreated cells. OD<sub>495</sub> of unstimulated cells was 0.29 ± 0.06 for sPLA<sub>2</sub>-IIA and 0.24 ± 0.03 for the sPLA<sub>2</sub>-IIA mutant experiments in panel A and 0.24 ± 0.03 for panel B. \* p<0.05 vs untreated control by one-way ANOVA. Data are representative of three separate experiments. (C). LNCaP cells were grown as above and stimulated for 72 hours with

sPLA<sub>2</sub>-IIA (1 nM) in the absence (dotted lines) and presence (solid lines) of the sPLA<sub>2</sub>-IIA inhibitor cFLSYR (SEQ ID NO: 6) (100 nM). Cells (1x10<sup>6</sup>) were assayed by flow cytometry following treatment with propidium iodide as described in Materials and Methods. Statistical analysis was performed on 10,000 events per sample. Data are representative of three separate experiments.

Please delete the paragraph on page 29, lines 8-21 and replace it with the following paragraph:

*RT-PCR.* Total cellular RNA was isolated from LNCaP, DU145 or PC-3 cells using the Trizol reagent (Life Technologies, Inc.). First-strand cDNA was synthesized from 5 µg of RNA with the cDNA preamplification system (Life Technologies, Inc.) using SuperScript II reverse transcriptase and an oligo (dT) primer. This was used as the template in standard PCR reactions using Amplitaq DNA polymerase (Perkin-Elmer Life Sciences, Boston, MA). Amplification products were analyzed on 2% TAE agarose gels made with MetaPhor agarose (FMC BioProducts, Rockland, ME) and photographed under UV illumination. DNA ladders of 25 and 100 bp (Life Technologies, Inc.) were used as size standards. Primers were designed based on the human sPLA<sub>2</sub>-IIA mRNA (NM\_000300. 2) deposited in the GenBank database (National Center for Biotechnology Information, Bethesda, MD) and are as follows : forward: 5'-TTTGTACCCCAAGAACTCTTAC-3' (SEQ ID NO: 7), reverse: 5'-GGGAGGGAGGGTATGAGA-3' (SEQ ID NO: 8).

Please delete the paragraph on page 31, line 26 to page 32, line 9 and replace it with the following paragraph:

The lack of sPLA<sub>2</sub>-IIA expression in benign glands following androgen deprivation suggests that expression of sPLA<sub>2</sub>-IIA gene requires androgens. To verify that, we searched the 5'-flanking region of the sPLA<sub>2</sub>-IIA gene using MatInspector Release 5.3 (Genomatix), and found an androgen response element (ARE) GAGGTAAATGGTATTCTC (SEQ ID NO: 9) from -546 to -527. Secondly, we treated the androgen responsive human prostate cancer cell line, LNCaP, with various doses of androgens and measured sPLA<sub>2</sub>-IIA mRNA and protein levels by RT-PCR and ELISA (data not shown). Indeed, there was an increase in the level of sPLA<sub>2</sub>-IIA transcript following 1 nM androgen treatment. In contrast, we could not find an

ARE within 3 kb of genomic DNA in the 5-flanking region of the cPLA<sub>2</sub>-α gene. Androgen treatment had no effect on cPLA<sub>2</sub>-α mRNA and protein levels (data not shown). Together, these findings indicate that sPLA<sub>2</sub>-IIA, but not cPLA<sub>2</sub>-α expression is normally dependent on androgens and in AIPC sPLA<sub>2</sub>-IIA expression becomes androgen-independent *via* an as yet unknown mechanism.

Please delete the paragraph on page 32, line 25 to page 33, line 4 and replace it with the following paragraph:

We have previously shown that human sPLA<sub>2</sub>-IIA is dose-dependently inhibited by a pentapeptide sequence comprising residues 70-74 of the native sPLA<sub>2</sub>-IIA protein (<sup>70</sup>FLSYK<sup>74</sup>) (Tseng, A., *et al.*, (1996) J. Biol. Chem. 271: 23992-23998). Because of the inherent flexibility of the linear peptide sequence, inhibition was weak in *in vitro* activity assays. We have recently designed two novel cyclic peptides (Church, W. B. *et al.*), cFLSYR (**SEQ ID NO: 6**) and a cyclic peptide where F and Y are substituted with 2-naphthylalanine (c (2NapA) LS (2NapA) R). Both have shown significant improvement in potency over linear peptides. The potent stimulatory effect of exogenous sPLA<sub>2</sub>-IIA on prostate cancer cell number was completely blocked by the sPLA<sub>2</sub>-II inhibitor, cFLSYR (**SEQ ID NO: 6**) (Fig. 2B) at all concentrations tested.

Please delete the paragraph on page 33, lines 6-15 and replace it with the following paragraph:

We next used flow cytometric analysis to determine how sPLA<sub>2</sub>-IIA affects the distribution of LNCaP cells in different phases of the cell cycle. In sPLA<sub>2</sub>-IIA containing medium, the proportion of LNCaP cells in the G1 phase decreased from 74% to 62% with corresponding increase of cells in G2/M phase in comparison to untreated cells (Fig. 2C). In the presence of both sPLA<sub>2</sub>-IIA and its inhibitor (cFLSYR) (**SEQ ID NO: 6**), the proportion of cells in G1 and G2 phase returned to basal levels (Fig. 2C). These results establish the biological importance of the sPLA<sub>2</sub>-IIA enzyme activity in prostate cancer cells and demonstrate that sPLA<sub>2</sub>-IIA-induced cell growth can be attributed at least partly to an increased proportion of cells entering G2/M phase from G1 phase.

Please delete the paragraph on page 34, line 20 to page 35, line 2 and replace it with the following paragraph:

To test the effect of blocking endogenous sPLA<sub>2</sub>-IIA on cell growth, we firstly determined the basal mRNA levels of sPLA<sub>2</sub>-IIA in 3 human prostate cancer cell lines. The androgen-independent cell lines PC-3 and DU145 cells were included in the study to also exclude a possible general toxicity of the inhibitors. mRNA encoding sPLA<sub>2</sub>-IIA was undetectable in DU-145 compared with LNCaP and PC-3 cells (Fig 4A). We then tested the effect of individual inhibitors cFLSYR (SEQ ID NO: 6) and c(2Nap)LS(2Nap) R on cell growth over a range of doses (1-100 nM). The proliferation of LNCaP and PC-3 cells was significantly decreased, and the smallest effective dose was 1 nM for both inhibitors (Fig. 4B). In contrast, neither of the inhibitors had an effect on DU145, presumably due to the lack of endogenous sPLA<sub>2</sub>-IIA. The low but effective dosage and its specificity for cell lines containing endogenous sPLA<sub>2</sub>-IIA only, indicate that non-specific cell toxicity is not likely to explain the inhibitory effect.